

## ENT COOPERATION TREA . /

From the INTERNATIONAL BUREAU

**PCT**NOTIFICATION CONCERNING  
AMENDMENTS OF THE CLAIMS(PCT Rule 62 and  
Administrative Instructions, Section 417)

Date of mailing: <b>30 May 1997 (30.05.97)</b>	To:  United States Patent and Trademark Office (Box PCT) Crystal Plaza 2 Washington, DC 20231 ETATS-UNIS D'AMERIQUE  in its capacity as International Preliminary Examining Authority
International application No.: <b>PCT/US96/15727</b>	International filing date: <b>27 September 1996 (27.09.96)</b>
Applicant: <b>THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK et al</b>	

The International Bureau hereby informs the International Preliminary Examining Authority that no amendments under Article 19 have been received by the International Bureau (Administrative Instructions, Section 417)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No.: (41-22) 740.14.35	Authorised officer:  H. Zhou Telephone No.: (41-22) 730.91.11
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## PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark  
Office  
(Box PCT)  
Crystal Plaza 2  
Washington, DC 20231  
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year)
30 May 1997 (30.05.97)

International application No.	Applicant's or agent's file reference
PCT/US96/15727	48231-A-PCT

International filing date (day/month/year)	Priority date (day/month/year)
27 September 1996 (27.09.96)	27 September 1995 (27.09.95)

Applicant
GREENWALD, Iva et al

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

21 April 1997 (21.04.97)

in a notice effecting later election filed with the International Bureau on:

\_\_\_\_\_

2. The election  was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No.: (41-22) 740.14.35	Authorized officer  H. Zhou  Telephone No.: (41-22) 730.91.11
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## PATENT COOPERATION TREATY

REC'D 07 JAN 1998

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## PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 48231-A-PCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US96/15727	International filing date (day/month/year) 27 SEPTEMBER 1996	Priority date (day/month/year) 27 SEPTEMBER 1995
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

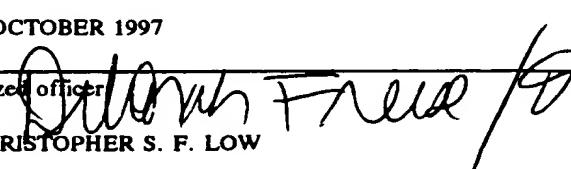
2. This REPORT consists of a total of 6 sheets.

This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of — sheets.

3. This report contains indications relating to the following items:

- I  Basis of the report
- II  Priority
- III  Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV  Lack of unity of invention
- V  Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI  Certain documents cited
- VII  Certain defects in the international application
- VIII  Certain observations on the international application

Date of submission of the demand 21 APRIL 1997	Date of completion of this report 07 OCTOBER 1997
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer  CHRISTOPHER S. F. LOW
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US96/15727

**L Basis of the report**

1. This report has been drawn on the basis of (*Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments*):

the international application as originally filed.

the description, pages 1-79, as originally filed.  
pages NONE, filed with the demand.  
pages NONE, filed with the letter of \_\_\_\_\_  
pages           , filed with the letter of \_\_\_\_\_

the claims, Nos. 1-86, as originally filed.  
Nos. NONE, as amended under Article 19.  
Nos. NONE, filed with the demand.  
Nos. NONE, filed with the letter of \_\_\_\_\_  
Nos.           , filed with the letter of \_\_\_\_\_

the drawings, sheets/fig 1-5, as originally filed.  
sheets/fig NONE, filed with the demand.  
sheets/fig NONE, filed with the letter of \_\_\_\_\_  
sheets/fig           , filed with the letter of \_\_\_\_\_

2. The amendments have resulted in the cancellation of:

the description, pages NONE.

the claims, Nos. NONE.

the drawings, sheets/fig NONE.

3.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the **Supplemental Box Additional observations below (Rule 70.2(c))**.

4. Additional observations, if necessary:

NONE

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.  
PCT/US96/15727**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The question whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

the entire international application.

claims Nos. 22-64 and 66-86

because:

the said international application, or the said claim Nos. \_ relate to the following subject matter which does not require international preliminary examination (*specify*).

the description, claims or drawings (*indicate particular elements below*) or said claims Nos. \_ are so unclear that no meaningful opinion could be formed (*specify*).

the claims, or said claims Nos. \_ are so inadequately supported by the description that no meaningful opinion could be formed.

no international search report has been established for said claims Nos. 22-64 and 66-86.

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US96/15727

**V. Reason d statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. STATEMENT**

Novelty (N)	Claims <u>17-19 and 65</u>	YES
	Claims <u>1-16, 20, and 21</u>	NO
Inventive Step (IS)	Claims <u>none</u>	YES
	Claims <u>1-21 and 65</u>	NO
Industrial Applicability (IA)	Claims <u>1-21 and 65</u>	YES
	Claims <u>none</u>	NO

**2. CITATIONS AND EXPLANATIONS**

Claims 12 and 13 lack novelty under PCT Article 33(2) as being anticipated by the disclosure in the Database dbEST, Release 072795, 27 July 1995, National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health, GenBank Accession number H19012, Name H19012, ENTREZ Document Retrieval System, Release 18.0, 15 August 1995. The reference disclosed an expressed sequence tag (EST) with at least 15 nucleotides identical to a polynucleotide encoding SEL-12. The complementary strand hybridizes thereto and the disclosed EST is a DNA.

Claims 1-16, 20, and 21 lack novelty under PCT Article 33(2) as being anticipated by the disclosure in the Sherrington et al. (1995) Nature 375: 754-760 reference which disclosed DNA encoding a protein which is effectively identical to that of *sel-12* (see figure 3 and the attached alignment of the sequence), obtained RNA expressed therefrom (RNA is expressed from an operatively linked promoter), see page 756.

Claim 14 lacks an inventive step under PCT Article 33(3) as being obvious over Database dbEST, Release 072795, 27 July 1995, National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health, GenBank Accession number H19012, Name H19012, ENTREZ Document Retrieval System, Release 18.0, 15 August 1995. The reference disclosed an expressed sequence tag (EST) that has at least 15 nucleotides identical to that of SEL-12. The complementary strand hybridizes thereto and the expression product of the EST is an RNA.

Claims 1-21 and 65 lack an inventive step under PCT Article 33(3) as being obvious over Sundaram et al. (1993) Genetics 135: 765-783 taken with Sherrington et al. (1995) Nature 375: 754-760, and the Stratagene Cloning Systems Catalog.

Sundaram et al. disclosed genes encoding suppressor and/or enhancer of *lin-12* activity (see at least the abstract) but did not explicitly disclose DNA encoding *sel-12*, however, the Sherrington et al. reference disclosed a DNA encoding a protein (Continued on Supplemental Sheet.)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US96/15727

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The description is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 5 because it fails to contain an adequate written description of nor adequately enable the practice of the claimed invention as to the plasmids defined by ATCC accession numbers 97278 and 97297. The plasmids are defined in the claims only by accession number and it is not apparent from the claims as to what the functional features of the plasmids are but for the inserted gene. In order to practice the full scope of claims 18 and 19, the identical plasmid is required and a requirement for deposit is made in accordance with PCT Rule 13<sup>bd</sup>.

Claims 18 and 19 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because practice of the claimed invention is not adequately described in writing, as required under PCT Rule 5.1(a)(iii), for the reasons set forth in the immediately preceding paragraph; and, claims 1-28 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because practice of the claimed invention is not enabled as required under PCT Rule 5.1(a) for the reasons set forth in the immediately preceding paragraph.

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US96/15727

**Supplemental Box**

(To be used when the space in any of the preceding boxes is not sufficient)

*Sheet 10*

Continuation of: Boxes I - VIII

**CLASSIFICATION:**

The International Patent Classification (IPC) and/or the National classification are as listed below:

IPC(6): C07H 21/04, 21/02; C12N 15/12, 15/70, 1/21 and US Cl.: 536 / 23.5, 24.31, 24.33, 25.1  
435 / 320.1, 252.3**V. 2. REASoNED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):**

which is effectively identical to that of *sel-12* (see figure 3 and the attached alignment of the sequence), obtained RNA expressed therefrom (RNA is expressed from an operatively linked promoter), see page 756. Here it is obvious to have combined the teachings of the cited references to obtain the *C. elegans* DNA as the Sherrington *et al.* reference indicated (page 760) that the gene has a homologous counterpart in, for example, *C. elegans*. Here, the Sundaram *et al.* reference indicated to one of ordinary skill in the art a process for determining/identifying genes where it is obvious to that polynucleotides from *C. elegans* that hybridize to the polynucleotide disclosed in the Sherrington *et al.* reference is a polynucleotide from *C. elegans* that encodes the same functional protein and is the *sel-12* gene and encodes the protein SEL-12. Here, the Statagene Catalog is indicative that expression vectors are known and used and would have been obvious to have had the gene put into same for expression of the DNA. Thus, the claims lack an inventive step.

**NEW CITATIONS**

SHERRINGTON *et al.* "Cloning of a gene bearing missense mutations in early onset familial Alzheimer's disease. Nature 29 June 1995, Vol. 375, pages 754-760.



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> :	A1	(11) International Publication Number: <b>WO 97/11956</b>
<b>C07H 21/04, 21/02, C12N 15/12, 15/70, 1/21</b>		(43) International Publication Date: 3 April 1997 (03.04.97)
<p>(21) International Application Number: PCT/US96/15727</p> <p>(22) International Filing Date: 27 September 1996 (27.09.96)</p> <p>(30) Priority Data: 60/004,387 27 September 1995 (27.09.95) US</p> <p>(60) Parent Application or Grant (63) Related by Continuation US 60/004,387 (CIP) Filed on 27 September 1995 (27.09.95)</p>		<p>(81) Designated States: AU, CA, JP, MX, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p><b>Published</b>  <i>With international search report.  Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(71) Applicant (for all designated States except US): THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK [US/US]; West 116th Street and Broadway, New York, NY 10027 (US).</p> <p>(72) Inventors; and  (75) Inventors/Applicants (for US only): GREENWALD, Iva [US/US]; Apartment 11B, 300 Riverside Drive, New York, NY 10025 (US). LEVITAN, Diane [US/US]; 53 Newcomb Road, Tenafly, NJ 07670 (US).</p> <p>(74) Agent: WHITE, John, P.; Cooper &amp; Dunham L.L.P., 1185 Avenue of the Americas, New York, NY 10036 (US).</p>		

(54) Title: IDENTIFICATION OF sel-12 AND USES THEREOF

## (57) Abstract

This invention provides an isolated nucleic acid molecule encoding a SEL-12. This invention further provides an isolated nucleic acid molecule which encodes a mutated SEL-12. This invention also provides an isolated nucleic acid molecule which encodes a mutated SEL-12, wherein the mutated SEL-12 contains at least one of the following: position 115 is a leucine, position 132 is an arginine, position 215 is a glutamic acid, position 229 is a valine, position 254 is a valine, position 255 is a valine, position 371 is a valine, position 387 is a tyrosine, position 104 is an isoleucine or position 204 is a valine. This invention further provides different uses of these nucleic acid molecules. This invention also provides different sel-12 mutants and transgenic animals which carry wild-type or mutated sel-12.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US96/15727

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) :C07H 21/04, 21/02; C12N 15/12, 15/70, 1/21

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X —	LEVITAN et al. Facilitation of lin-12 -mediated signalling by sel-12, a Caenorhabditis elegans S182 Alzheimer's disease gene. Nature. 28 September 1995, Vol. 377, pages 351-354, see entire document.	1, 2, 4-17, 20, 21, and 65
Y	STRATAGENE CLONING SYSTEMS CATALOG, issued 1993, La Jolla, CA pages 27, 31, 2 and 313, see entire document.	3, 18, and 19
Y	SUNDARAM et al. Suppressors of a lin-12 Hypomorph Define Genes That Interact With Both lin-12 and glp-1 in Caenorhabditis elegans. Genetics. November 1993, Vol. 135, pages 765-783, see entire document.	18 and 19 1-21 and 65

Further documents are listed in the continuation of Box C.  See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
* "A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
* "E" earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
* "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
* "O" document referring to an oral disclosure, use, exhibition or other means		
* "P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

18 DECEMBER 1996

Date of mailing of the international search report

21 JAN 1997

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Authorized officer

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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US96/15727

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database dbEST, Release 072795, 27 July 1995, National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health, GenBank Accession number H19012, Name H19012, ENTREZ Document Retrieval System, Release 18.0, 15 August 1995, see entire document.	12, 13
-		_____
Y		14, 15

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US96/15727

**A. CLASSIFICATION OF SUBJECT MATTER:**

US CL :

536 / 23.5, 24.31, 24.33, 25.1

435 / 320.1, 252.3

**B. FIELDS SEARCHED**

Minimum documentation searched

Classification System: U.S.

536 / 23.5, 24.31, 24.33, 25.1

435 / 320.1, 252.3

**B. FIELDS SEARCHED**

Electronic data bases consulted (Name of data base and where practicable terms used):

Automated Patent System - USPAT, JPOABS, EPOABS

DIALOG FILES - 5, 11, 73, 76, 144, 155, 156, 185, 434, 440, 444, and 636

Search Terms - sel-12, Caenorhabditis elegans, suppress, enhance, ar131, ar133, and ar171

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US96/15727

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  **Claims Nos.:**  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  **Claims Nos.:**  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3.  **Claims Nos.:**  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
1-21, 65

**Remark on Protest**  

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.